VACCINE AND VARIOLA.*

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The practitioner who has at his command material eminently adapted for scientific research, material which in importance and fulness can hardly be matched anywhere, should make it his first duty to render it accessible to the profession at large. This is my excuse for presenting the following work, though well aware, that in matters of vaccination especially, "in writing foolish books there is no end." I am the more strongly induced to do so because of late the call for confirmation or rectification of views accepted until lately, has become stronger on account of new experiments, and because I believe I am able to contribute, in some degree, to the elucidation of many contradictory views:

1. VARIOLA-VACCINE.

The question of the origin of vaccine, considered in the nature of the relations between variola and vaccine, is as old as the use of protective inoculation, but it remains yet to be solved. Even the communications of Tschamer who attributed the causes of variola and vaccine to *Penicillium olivaceum*, a fungus found upon pine leaves, do not settle the question, even if his theory were confirmed. From Jenner's theory that cow-pox originated in horse-pox, the more comprehensive theory was further evolved, that variola as well as the pox of other animals had all one common origin. So that cow-pox and horse-pox were supposed to be the specific representatives of a variola modified by the peculiar nature of these animals. In other words, that vaccine is nothing more than the variola virus transformed in the body of the animal.

In opposition to this theory, lately maintained by Bollinger, some French savants, and in England of late, Fleming maintain the view that though variola and vaccine are related to one another, still they cannot pass one into the other, and that vaccine cannot be produced by variola.

I must mention, among others, the Report of the Commission

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appointed to investigate this question in Lyons (Vaccine et Variole par M. Chauveau, etc., Paris, 1865). This commission provided with such rich material and competent investigators, that a definitive result was to be expected, reached indeed conclusions which left nothing to be desired in so far as clearness is concerned, conclusions which in practice would amount to the fact: that it were useless to attempt the production of animal vaccine from variola humana. But in this report, however lasting and important it may be for science, there is a great mistake, a result of the ignorance of the thoroughness and worth of former experiments in the same direction. The report declares as inaccurately observed the positive results of those investigators, who undoubtedly succeeded in propagating vaccine from variola. It is not every description of such propagation that will bear scrutiny, but some will bear the light of the most searching criticism. Thus the assertions of Thiele at Kasan, lack necessary clearness on the certainty of his success in obtaining variola vaccine; but the statements of Ceely, Reiter, Badcock, Senft, will bear the closest investigation.

The variola-vaccine, produced in 1839 by Ceely was extensively propagated. It was carried from England to Hanover and the physician Schneeman from that place, remarks somewhat disapprovingly about a year afterward, that the virus obtained from it offers no advantages, and presents no differences from the common humanized lymph. Thus giving Ceely's variola-vaccine the very best testimony; it had become true vaccine.

So then the production of vaccine virus from variola virus is, under certain conditions, possible, but it succeeds seldom, and we are still ignorant of the laws according to which this change either takes place or does not.

We know, as the above mentioned report of the Lyons Commission has established it, that in most cases the variola humana inoculated to horses and cows does not produce true vaccine, and that the virus produced by this inoculation when reinoculated on the human subjects, may occasionally return to varioloid.

We know further that such variola equina or bovina is not generally transmitted in a lasting manner, even when the virus is carefully inoculated from one animal to the other.

On the other side we find in the literature of the subject several

descriptions of epizoöties, which we must almo t undoubtedly consider as the small-pox of animals, because the inoculation of the virus from the pustules of these animals occasionally caused severe cases of variola.

From this we have three forms of small-pox in cattle :

1. That epizoötic, which although not yet produced experimentally, has been repeatedly observed and described; which may be communicated from animal to animal and must be held as variola because it produces variola in man.

2. The variola inoculated to cattle, which does not become vaccine, dies out in the second or third generation and maintains at first the character of variola.

3. The variola-vaccine, which may be propagated and becomes vaccine.

The investigation of the virus of the first form, in epizoötics seems of lesser importance for practice, and it may not only be difficult but also quite a serious matter to originate purposely such an epizoötic.

The variola equina and bovina of the second form is thus far not a subject of controversy, and I shall revert to it hereafter.

The question of variola-vaccine is the subject of discussion, and whether cow-pox is dependent or not upon variola humana. Indeed the contention of the different theorists is so violent that in the summer of 1880 a meeting of the Academie de Médicine, in Paris, was adj urned by the President on account of the violence of the debates upon this question.

If we consider closer the question of the origin of cow-pox we may admit as settled, that cattle have not the property of propagat ng from year to year the virus (contagium), for vaccine is propagated with much greater difficulty among cattle than among men, and humanized vaccine has never yet spread spontaneously or without procatarctic cause. So that without objective favorable causes among cattle, cow-pox which is still found occasionally, would, long ago, have ceased to exist.

Therefore, we must come to the conclusion that vaccine originates in an infecting material (virus) which is propagated independently of the cattle, which comes on them different ways, and infects them with different degrees of intensity according to the higher or lower potential form with which they are attacked.

In the infection of cattle with the virus of variola humana we look for a cause for vaccine, and for a very powerful one.

It would be of great importance for the practice if this very infection, if this mode of breeding (?) of vaccine from variola were thoroughly investigated. Then on the breaking out of an epidemic of small-pox at a place not provided with vaccine, this want could be immediately remedied by procuring out of the small-pox lymph itself, on cattle everywhere to be found, the proper agent for protection. If we consider, for example, that in Spanish America there is a constant need of such an agent, that in the East even to this day direct inoculation is still flourishing, we cannot but desire that the question: How is good vaccine to be generated? should be settled as promptly as possible.

Thinking I am better acquainted with animal vaccine than many other physicians, I have recently attempted this question when occasional cases of small-pox occurred in Hamburg, and have had the good fortune of producing variola-vaccine. Such experiments are expensive and take time besides being a work of great responsibility, yet my labors were rendered easy, as I had at my disposal the stable and overseer of the vaccine establishment. I was granted the privilege of disposing of a few extra animals for this object and found ready support on the part of my colleagues in the establishment and in the general hospital, in observing the effect of the new inoculated matter upon human subjects, under the control of the hospital physicians.

I made use of the calves which were sent from the cattle market to the vaccine establishment They were from three to four months old, and probably, on account of their age, free from previous vaccine-invasion. I selected the best fed subjects, made no selection as to sex or color, and fed them with 10 litres of milk daily. I could not and would not follow in everything, the directions given by Thiele for the production of variola-vaccine, because I hold them to be too comprehensive. Thiele, for example, prescribes that a cow should be taken from four to six years old, fresh in milk, of a light color, that she should be inoculated behind the udder on a shaved spot, with an incision not too shallow; with that he directs that clean variola lymph should be taken out of pustules having still a pearly color and thin; if the animals were kept at a tempera-

ture of 15° C., it would be expected that every third lancet puncture would produce a pustule. The contrast between these statements and those of the results obtained by other investigators is, as can be seen, enormous. Thiele's account is, however, so short, he goes so little into the details of what was actually observed, that his statements lose considerably of their weight. Thiele has evidently made no observations upon the property of transmission of pox efflorescence from cow to cow, or he must have noticed, and assuredly mentioned how important the difference is between the strikingly great power of transmission of the fully developed pustule of variola-vaccine and the feeble power of the more undeveloped pimples.

Had Thiele directed his attention upon this point, the contrast between his assertions and those of later observers, of Chauveau, for example, could scarcely have been so great, for Chauveau maintains the production of vaccine out of variola, as simply impossible.

Besides the observations of Chauveau and his associates, other investigators have been satisfied with carrying over immediately the variola-vaccine produced experimentally, to the human subject.

There is nowhere the question of more extensive breeding from calf to calf or from cow to cow.

The only one, who so far as I know, witnessed the change of variola-vaccine produced by intentional inoculation, into cow-pox, is Reiter (Jahrb. des ärtzlichen Vereins in München, III, Vol.) who made, following exactly the directions of Thiele, a new attempt in the transfer of variola upon cows, after having failed during the ten preceeding years, in fifty different experiments. He raised a pustule with the contents of which he inoculated a child. Accordingly he saw on the tenth day, fever arise, and on the twelfth the suspicious symptoms of varioloid, that is to say, fifteen discrete pustules, so that he desisted from further use of this ymph. But in the cow stable, in which the above mentioned cows were kept, Reiter observed after three weeks, true cow-pox, which transferred to the human subject acted like vaccine and could be inoculated again and again. So that Reiter's variola-vaccine had become animal vaccine within four generations at the outside.

This experiment gave me a hint as to the application of variola-vaccine in general. It is evidently a serious matter to use it in the first generation, for, as in the Eastern inoculation, varioloid might

be produced. It is more proper to train it first through a few cows. in order to have vaccine suitable for practice. The germs of variola humana, intensely active and endued with great tenacity of life, form, when impregnated in the tissues of living cattle, pustules somewhat similar to those of small-pox. Therefore, I should not be astonished if the lymph of such pustules should still contain, after five or six days, unchanged germs of variola, germs which, later on, after repeated passages through animals, would assume a milder form and become modified.

I will now revert to the experiments of the Lyons Commission, with which the following description of my three unsucessful experiments in obtaining vaccine, fully agree, experiments which I have undertaken to control the previous inoculation of another calf which was immediately followed by success.

Experiment I.—On May 11th, a white and black bull calf, weighing 254 pounds is inoculated with varioloid lymph at the scrotum with (flat) superficial incisions. The lymph had been obtained two days before, and filled in tubes from the varioloid pustules (on a woman 35 years old, vaccinated when a child,) on the sixth day after the first appearance of the small-pox eruption.

Temperature at time of inoculation, 39.5.

After.	Morning.	Evening.	
1×24 hours	39.4	39.6	
2×24 "	39.6	39.4	Appetite lessened.
3×24 "	39.5	39.6	Flatulence, stool greenish, i. e., bowel symptoms usual after the vaccination of calves. The incisions but little inflamed, somewhat prominent, seem nearly all tending to the formation of pustules.
4×24 "	39.4	39.3	Some places abort, others enlarge and look very promising. Nearest the scrotum upon the shaved parts, small papulæ with yellowish centre, develop on the opposite side of the incisions.
5×24 "	39 5	39.6	Flatulence ceased, every thing seems to abort.

After.	Morning.	Evening.	
6×24 hours	39.3	39.2	Upon the inoculated spot and
7×24 "	39.4	39.3	the neigbborhood of the scrotum the papulæ have become small globular pimples, with amber colored scab and a somewhat reddish rim.
8×24 "	39.2	39.1	Two small new papulæ have formed on the abdomen, which from their position may have originated from two pimples on the scrotum by direct contact through penetration of the lymph into the skin.
9×24 "	39.3	39.2	The calf weighs 258 pounds, an increase of four pounds.
10×24 "	39.2	39.4	The last two papulæ have also become small pimples. The
11×24 "	39.3	39.2	other pimples have not enlarged, but have become drier and darker.
12×24 "	39.4		The scabs have mostly fallen off. The calf is sent away.

Experiment II.—A handsome black and white male calf, ten weeks old, had remained one day in the stable and was fully rested from transportation, weighed 166 pounds at the time of inoculation. The lymph had been obtained from a case of confluent variola. It was perfectly limpid and had lain for one day between glass plates sealed with paraffine; a second charge was drawn one day later into a tube as the pox was already getting hemorrhagic. The second charge was already somewhat yellow, turbid and a little bloody and was used almost immediately.

The first charge (I) was applied in 27 flat (shallow) incisions on the perineum, behind the scrotum; in the second charge (II) in 21 incisions on the scrotum.

Temperature on day of inoculation 39.5.

After.	Morning.	Evening.	
1×24 hours	39.5	39.4	The lymph of I seems to be active, that of II not.

After.	Morning.	Evening.	
2×24 hours	39.6	39.8	The animal is affected, but presents otherwise no striking symptoms.
3×24 "	39.5	39.7	The calf is more active, there is some reäction at the scrotum. Diarrhœa.
4×24 "	39.4	39.5	The incisions of I prove a beginning of papulæ, which have little elevation and are of small capacity. At the scrotum the reäction is greater.
5×24 "	39 5	39 4	Diarrhœa subsided. The inoculation incisions at the scrotum have become reddish pimples which bear upon higher and somewhat papulous centre a scab about 3 mm. broad.
6×24 "	39.3	39.4	Neither inoculated surfaces have produced any pustules; the pimples discharge, with blood, abundant viscid serum, when squeezed with pincers.
7×24 "	39.4	39.3	The pimples get drier.
8×24 "	39.2	39.4	Everything disappears from
9×24 "	39.5	39.3	the inoculated surface on the perinæum, and two days later this surface shows nothing but small, sharp little crusts. But on the scrotum the pimples extend over the reddish ground, and in their neighborhood other small pimples are formed, full of matter, which contained, as the sequel proved, an entirely inactive matter.
10×24 "	39.4	39.2	The pimples on the scrotum
11×24 "	39.4	39.3	and neighborhood still increasing, and are moist.

After.	Morning.	Evening.	
12×24 hours	39.3	39 2	They become dry scabs.
13×24 "	39.4		These scabs become loose and must fall within two or three days.
			The calf is sent away with an increase in weight of 6 pounds.

Here very powerful variola produced no vaccine in the calf, but on the sixth day after inoculation, the calf was already protected against vaccine, for it was on that day inoculated with especially active calf's lymph without result, with a lymph which applied at the same time upon another calf succeeded splendidly in the latter case.

With fresh lymph taken on the sixth day from the juicy pimples of this animal I inoculated immediately another calf with 32 incisions and puncture.

Experiment III.—After three days the inoculation seems inactive. After six days everything dries up without results, but on the seventh day, the inoculated surfaces grow more elevated and succulent, to dry up on the following day. The insignificant looking scabs are allowed to fall on the fourteenth day.

This very same calf was on the day after inoculation, also inoculated with the lymph of the first generation of mature variola and vaccine. Seven incisions were loaded in the contents of a tube filled one month before; from this, seven fine pustules formed, and with the contents of these pustules a child was vaccinated (see below). No fever was observed in this calf either, the temperature reached on the third day only 39.6, and the general symptoms were very similar to those of its mates.

From the above is seen that I observed exactly the same thing as Chauveau. The animals with moderate bowel symptoms show no important febrile signs, and from the second day a trifling reäction inducing the slow formation of little pimples. The pimples increase in size, infect somewhat their surroundings by contact, and form scabs from the 12th to the 17th day There is no where to be found any further eruption either on the hairy or on the bare surfaces.

Chauveau considers this process as true variola bovina, and the

same follows indeed generally the inoculation of the cow. I hold this form as abortive, as compared with true variola-vaccine. The pimples are similar to those of abortive forms which are met with among cattle who have taken cold or with re-vaccinated human subjects. If we were to attempt the further inoculation from papulæ and pimples produced by re-vaccination, we would certainly observe a feeble result on the human subject. But with cattle which possess so little sensibility to pox virus, only the lymph taken from perfect pustules takes well. Therefore we cannot expect true vital energy to result from the contents of such pimples These pimples must also form a scab earlier than the variola-vaccine pustules, for all vaccinal abortive forms run a more rapid course than the normal.

Lastly, I do not regard it as a criterion of these special forms. that they should, as Chauveau insists, possess the property to give back variola to the human subject, under certain conditions for even the use of true variola-vaccine in the first generation (see Reiter above) is not without danger.

So then the pimples are abortive forms. I will now describe the production of variola-vaccine.

If variola and vaccine are inoculated simultaneously upon the same subject, the two germs of infection do not disturb one another, they both develop according to their kind. This is a fact generally recognized and also by Chauveau (Chauveau Vaccine et Variole, p. 65). Therefore, I could use for the inoculation of variola a calf that was serving for the production of animal vaccine for the public, if I only chose for the place of application of the new virus, one sufficiently distant to avoid with certainty the mixing of the two kinds of lymph. The result justified my proceeding, for our old vaccine continued to succeed well, alongside of the variola-vaccine pustules which were developing.

It might be indeed objected to, that in such experiment the proof is not conclusive that vaccine may be produced from variola, that perhaps vaccine has penetrated into the surface of insertion of variola, and that we have simply to deal with a mixed form. But, besides that, I have neglected nothing to prevent every mixture; if there had been such a mixture, that could have produced only, either variola bovina or vaccine, or both simultaneously and side by

side. But here there were formed neither the pimple, which is taken for variola bovina by the supporters of the duality of both infective matters, nor ordinary animal vaccine, but a pustule with very active lymph which was weakened gradually into common animal vaccine and with the properties of original animal vaccine and with the properties of original cow-pox, exactly as it was described by Ceely and other investigators.

I succeeded immediately in the first experiment, but only in this one; the subsequent experiments produced nothing but abortive forms, as I have already described.

I obtained on the 27th of April, from about eight pustules, which were already looking somewhat turbid, a capillary tube full of good, and somewhat yellowish lymph, from a workman 25 years old who had been vaccinated when a child and had three inoculation scars, and had been seized on the 23d of April, 1881, with a discrete eruption of varioloid. I transferred these about twenty hours later, on April 28th to a female calf on the left side of her hypogastrium, which had been shaved shortly before, by means of five flat, scratched, incisions.

In this, I proceeded in the following manner: I blew the whole contents of the tube, a pretty large drop of lymph upon one spot of the inoculating surface and with that drop I moistened the lancet, which I applied at first to the other incisions; at last I scarified the surface upon which the lymph had been blown, and it was at this very spot that the variola-vaccine originated.

This calf was immediately inoculated with animal lymph that had been collected 6×24 hours before, on a sufficiently distant part of the body, which inoculation, just because it had not been performed with lymph of the fifth day, did not produce brilliant results, but still gave rise to pustules, the contents of which inoculated later to children, gave a good result. Therefore it cannot be said, that here the vaccine had been influenced by the variola. The calf had already been two days in the stable had fully rested from transportation and at the time of inoculation had the normal temperature of 39.2 Its skin was tender and became red by shaving.

After.	Morning.	Evening.	
1×24 hours	39.6	39.8	Both vaccine and variola seem to thrive.

After.	Morning.	Evening.	
2×24 hours	39.2	39.3	Stool, as customary after vaccination, somewhat thin.
3×24 "	39.3	39.4	Stool mushy. Appetite good.
4×24 "	39.3	39.2	The same. Vaccine acts mildly. Variola still very young.
5 24 "	39 2	39.2	Stool better. Appetite good. Of the vaccine applied the greater part has aborted, but yet many good pustules have formed. Of the five places inoculated with variola, four can hardly be recognized, the reäction has altogether come to naught. The fifth spot bears a flat pustule without umbilication, 4 mm. in size, round and yellowish-white.
6 24 hours	39.2	39.3	This pustule is now six millimetres, pearly, with hardly any redness on the edge. A little depressed in the centre, it is somewhat smaller but exactly of the color of the pustule described by Ceely, table 10. With the lymph of this pustule another calf is inoculated, and the pustule cut out for microscopic investigation.
7 24 "	39.1	39.2	The successful vaccine pustules are in part already purulent. The calf seems to be doing well, has a good appetite and regular digestion.
8 24 "	39.2	39.1	The calf remains healthy.
9 24 "	39.1		The vaccine pustules have scabbed. Between them are little pimples covered with scabs.

After.	Morning.	Evening.	
			Similar small pimples, and scabs but much closer together, and almost herpetically confluent, are in the neighborhood of the variola-vaccine pustule. All these forms have been, evidently produced by the influence of the vaccine upon the skin irritated by shaving, and also somewhat excoriated. Besides there are also a few fresh papulæ between the vaccine scabs, produced by self-inoculation, from the ripe vaccine pustules, as the matter was taken from it where the pressure of the pincers had somewhat loosened the epidermis.
10×24 hours	39.2	39.1	These papulæ are also covered with scabs.
11×24 "	39.0	39.1	At no place distant from the inoculating surface are there any traces of secondary exanthema. The vaccine scab became loose. The surface previously occupied by the variola-vaccine pustule is covered with a black scurf.
12×24 "	39.1	39.2	The calf is sent away in good condition.

FURTHER BREEDING OF VARIOLA-VACCINE.

Second Generation.—As I reinoculated on the sixth day the scant lymph taken from the inconsiderable pustule produced by inoculation, I was in the highest degree of expectation, to see how it would operate.

The lymph, and that one alone, was used fresh and by means of

six flat incisions, in front, behind and on the scrotum of a bull calf about three months old. Temperature on day of inoculation 39.4.

After.	Morning.	Evening.	
1×24 hours	39.3	39.3	The animal has somewhat more diarrhœa than the one from which the virus was taken.
2×24 "	39.4	39.5	Diarrhœa watery.
3×24 "	39.4	39.6	" "
4×24 "	39.3	39.5	Reaction at all inoculated spots.
5×24 "	39.4	39.6	Twenty-one pustules all equally well developed, contain somewhat thinner matter than our previous animal lymph. They look like vaccine pustules of the very best quality.
6×24 "	39.5	39.4	The pustules have increased in size, are rather duller in color and contain abundant and clear matter. No accessory pimples, no general exanthema.
7×24 "	39.5	39.6	The pustules resemble vaccine pustules of the fifth day that have quickly matured, are very large and of beautiful pearl white. In the middle they bear a somewhat depressed scab, with this their contents is clear serum, and they are surrounded by sparingly reddish borders. The body of the *calf is puffed.* Some little diarrhœa; begins to decrease on the eighth day.
8×24 "	39.4	39.3	The pustules which are getting more dull in color are still whitish, and still contain limpid matter. The centre scab is getting larger.

After.			Morning.	Evening.	
9×24	hours		39.2	39.4	Still some diarrhœa.
10×24		"	39.3	39.5	The centre scabs have become harder.
11×24		"	39.4	39.3	No secondary exanthema, favorable general health.
12	24	"	39.2	39.4	Near the scrotum are to be seen four abortive little pimples evidently caused by over-inoculation in contact; they assume
13	24	"	39.2	39.5	the form which we are wont to see produced after auto-vaccination of children. They are
14	24	"	39.4	39.2	
15	24	"	39.1	39.2	round, raised, somewhat hard, the raised surface covered with flat yellowish scab surrounded
16	24	"	39.3	39.1	by a reddish border, exactly as described by Ceely, (see table 13 middle line.
17	24	"	39.4	39.3	The rim of the pustule is getting loose, the middle still holding fast. The scabs are beginning to break and may fall within two days.
18	24	"	39.2	39.3	
19	24	"	39.3	39.5	
20	24	"	39.4	39.2	

The calf presents no secondary symptoms, or further exanthema, and is now given away. Its pustules corresponded exactly to the figures of Ceely in tables 15 to 21; only Ceely's pustules were somewhat smaller and ripened one day later.

I had never yet seen pustules of so large a size upon our calves, and the lymph taken from them struck me on account of its abunddance and of its fluidity. Of its energy I was to convince myself by and by in developing the third generation.

Third Generation.—This calf was inoculated with fresh lymph from the pustules of the fifth and sixth day of the former calf, on

two successive days, every incision developed a pustule. This calf, otherwise well-fed arrived during such a violent rain, that it was 24 hours before it was completely dry. Under such circumstances our old vaccine would most probably have entirely or almost entirely failed. The temperature of this calf (at the time of inoculation 39.3) never passed 39.5, and even this was reached only on the 4th, 7th and 8th evening after inoculation. The animal had on the first day an attack of diarrhœa which lasted until the 7th day, maintained a good appetite and weighed before inoculation 140 pounds, and 15 days later 150 pounds.

The pustules produced with the younger lymph that had been applied one day earlier, succeeded better than those originating from the inoculation of the following day. The pustules of the first category became very fine, and after six days produced quite large *centre* scabs which increased gradually in size, still held after 15 days and fell probably on the eighteenth day, that is, four or five days earlier than on the second generation.

The pustules originating from the second inoculation of this calf remained weaker, smaller, with less fluid formed scabs earlier, (most of them on the fourteenth day) leaving a smooth cicatrix with few hairs. This calf also developed on the seventh day a few abortive reddish pimples at spots which admitted of a transmission contact from one of the pustules opposite ; but they remained smaller as compared with those of the former calf, on which they also did not make their appearance until five days later.

The above second and third generation was transplanted by myself with fresh lymph from calf to calf ; afterwards this lymph stock was kept up immediately, with preserved lymph and with this an almost fabulous activity was observed.

From this calf the *fourth generation* was obtained by means of lymph kept 19 days in tubes somewhat badly closed. Only few good pustules were produced on the fifth day, which grew in size during the following two days. The lymph taken from these was preserved six weeks in order to inoculate another calf.

Fifth Generation.—Two tubes furnished the lymph for 18 incisions, which produced nine pustules, which after 6 by 24 hours contained liquid yet quite limpid. This calf was also inoculated with our old vaccine, from imperfect pustules and with unsatisfactory results.

Sixth Generation.—Lymph of the former calf preserved for two days in a tube succeeded finely in every incision, while very good lymph of the old stock inoculated at the same time fresh from calf to calf succeeded only indifferently.

From this experiment, moreover, I have always raised simultaneously, both sorts of lymph upon the same calves, naturally with the necessary preautions against an intermixture. In this the old vaccine seemed to me, to be gaining in energy and freshness, as though it were excited by the powerful lymph of variola in its neighborhood, which on its side seem to approach, very slowly, it is true, the milder forms of the old stock.

The variola-vaccine pustules of the seventh and eighth generations had dried after 8 by 24 hours; these of the 10th which had, moreover, succeeded admirably, contained in some few pustules which had remained small, lymph still clear after 8 by 24 hours.

From this calf two more stock-fellows were inoculated, the *eleventh generation;* one with fresh lymph of the fifth day, the other, also, with fresh lymph, but of the eighth day. And while on the latter, out of six incisions, only two pustules were formed, the inoculation of the first, with the younger lymph succeeded admirably. So the younger lymph proved to be the stronger. The following five generations produced very good results; the sixteenth generation failed partly on a sickly calf.

Now, in December, having reached the twentieth generation, I can maintain that the difference between the new lymph, and the Beaugency lymph is entirely obliterated to an inexperienced eye.

Yet the lymph of the new stock develops with more certainty into full numbered, large and lasting pustules, which after 6 by 24 hours contain as yet no purulent matter; differently, then, from the lymph of our old stock, the pustules of which, after or within 6 by 24 hours, become purulent and inactive.

The lymph of the eighth day, of the new stock which at first was still very active, proved, in the eleventh generation, already somewhat uncertain, and in the nineteenth generation the fresh lymph of the seventh day proved a failure.

With this the further separate production of both lymph stocks is of no further interest, yet I will continue it until the introduction of the new lymph as the only matter inoculated at the vaccination establishment.

We are now coming to the results obtained with this lymph upon the human subject.

Because direct germs of variola humana might yet be suspected in the newly formed vaccine pustule formed from the pox lymph, inoculated five days previously on the calf, I held the transmission of the lymph at this first generation, as a dangerous experiment. Therefore, I inoculated only the lymph of the second generation, which, as you recollect, had been produced from the first generation with lymph preserved five weeks in a tube.

As there was no other subject on hand, I selected in the hospital, a yellowish looking child, which had been badly fed, had never been vaccinated, and was threatened by the epidemic of small-pox there; her skin was very sensitive and showed many scratches. From three inoculation incisions were produced on the seventh day, three very young vaccine pustules, of which the contents remained limpid five days, they dried on the twelfth day and healed with suppuration.

Temperature Scale.

	Morning.	Noon.	Evening.
On day of inoculation	37.3	37.5	37.5
1×24 hours after "	37.6	37.4	37.5
2 24 " " "	37.6	37.3	37.8
3 24 " " "	37.8	37.9	38.4
4 24 " " "	38.7	38.5	39.3
5 24 " " "	39.5	39.6	40.0
6 24 " " "	38.4	38.3	38.1
7 24 " " "	38.1	38.4	38.5
8 24 " " "	37.6	37.9	38.7
9 24 " " "	38.5	38.2	38.9
10 24 " " "	38.1	38.5	38.6
11 24 " " "	38.3	37.8	38.0
12 24 " " "	37.8		38.3
13 24 " " "	37.4		38.5
14 24 " " "	37.0		37.6

Already on the third day, then, before any local reaction on the inoculated surface, an acute eczema had appeared on the left knee, with fever going to 40°, this dried up within three days under a covering of salicyl cotton.

On the ninth day after vaccination axillary bubo on the inoculated arm. From the twelfth to the sixteenth day, six discrete reddish pimples form here and there, one of which became a subcutaneous fluctuating tubercle, which, however, disappeared as well as the other pimples in the course of a few weeks.

The temperature scale shows that the feared pox fever did not make its appearance on the 12th to the 14th day, nor did any variola eruption show itself, yet the six pimples were no common vaccinal symptoms. Therefore, we cannot say that the inoculation was a failure. The child was not especially fitted for the experiment on account of her skin.

After this I inoculated four more children with lymph of the third generation. One of them was vaccinated with lymph which had been preserved seven and seventeen days in a tube with somewhat defective sealing, both times without result.

With the other three, the 17 days old lymph proved effective, and it produced neither secondary fever nor general exanthema.

Frieda M., nine years old, undergoing a vapor bath cure on account of tophi (gravel ?). The inoculation incisions give within seven days four pustules, afterwards highly colored areola, painful axillary glands. During this time there is produced on the 3d day after vaccination an angina tonsillaris with a febrile course of three days. From the ninth day after vaccination the child is, and remains free from fever; no further exanthema.

N. V., one year old child with spondylitis. Within seven days nine incisions on the left arm produce eight pustules, besides which 4 more pimples appear. The pustules are rubbed away four days later, purulent. On the 12th day a young* pimple makes its appearance on the left inguinal fissure, which, as it seems, was inoculated there by the finger nail of the subject. This pimple, also secretes abundantly afterward. On the ninth day, diarrhœa begins, temperature rises to 38.8, to fall the following day to 38. On the 14th day there are on the inoculated surfaces gray ulcers, the size of a ten cent piece, which, three days later are the origin of a heavy attack of erysipelas. This passes away with the usual temperature curve.

Friederke H., 1½ years old, scoliatic. Nine incisions produce

*The word "young" which qualifies vesicle pimple, etc., in so many places, means new, fresh, recently-formed.

within seven days eight pustules, which dry up as customary. On the seventh day after vaccination it is attacked by a left side interstitial pneumonia, four days fever with remissions and a subfebrile state of several weeks duration.

The sickness of all three of these inoculated subjects during the development as well as during the ripening of the pustules may be explained by the extraordinary bad weather of those days, which may have been injurious to weakly patients under the influence of vaccine, rendering the children especially sensitive. It warns, however, to great caution in the use of variola-vaccine of the first generation, as of an uncommonly active lymph.

On this account I continued my experiments only at the eighth generation.

A child 1¼ year old, with a fracture of the femur pretty well healed, is inoculated in nine incisions with lymph one day old, preserved in a tube. At the usual time two pustules are produced, which heal in a natural manner but the child affected with cold in the head and cough has 4 by 24 hours after vaccination, an attack of measles. With this, two days' fever with remissions, which is followed by a subfebrile state lasting five days. This incident, and especially the rapid disappearance of the eruption gave me the suggestion that I had observed, those secondary phenomena observed so seldom after inoculation, as they are described by Behrendt, *Berl. Klin.*, 1881, p. 679. Lymph taken from the pustules of this child acted very well upon other children, but with nothing extraordinary.

At first variola-vaccine was not especially weakened by keeping in tubes, and on account of its limpidity was easily blown out of the tubes. The lymph of the later generations, however, took more and more the character of animal lymph, it coägulated easily and failed often. With tube lymph of the 13th generation, four days old, I produced from six punctures only one pustule, and in the hands of other physicians the results obtained with it were also often incomplete.

I did not offer this lymph to my colleagues until the ninth generation, and it was readily accepted. None of the gentlemen gave reports of unfavorable secondary symptoms; none observed either secondary fever or general exanthema.

After I had received no suspicious report from any one I inoculated immediately from calf to the human subject, lymph of the 15th generation obtained on the sixth day after inoculation. The effect was brilliant. By the end of the first week, a strong local as well as general reäction had taken place, but no other symptoms were noticed. As several children could not come for inspection on account of the strong reäction on the seventh day, the weather being bad, on later examination I could discover neither secondary fever nor general exanthema between the 10th and 14th day after vaccination. Yet it was not to be denied, that the local process took place with greater intensity, and that the scabs formed slower than ever before observed. I am satisfied that the scabs from many an arm did not fall before the 25th day, looking retrospectively upon the inoculation of calves and upon the application of the new lymph I came to the following conclusions:

Variola humana inoculated upon cattle produced commonly on exanthema in the form of pimples circumscribed on the inoculated surfaces, which passes away without much fever or other serious symptoms; and without general exanthema, which, moreover gives a lymph which is not suitable for reproduction among cattle. These pimples shed their scabs within 14 to 17 days, and represent, it is true, the common, but only the abortive, form of variola bovina.

In rarer cases, but with altogether similar symptoms, a pustule is formed instead of the pimple, the variola vaccine pustule, which requires an interval of three weeks and more for shedding its scabs, and which produces a lymph uncommonly active for reproduction.

It is the progenitor of an especially strong cow-pox and the most perfect form yet intentionally produced of variola bovina. The exanthema of the abortive form, as well as that of variola-vaccine, both contain a lymph which is suspected of harboring germs of variola that may be transmitted to man.

But while the abortive form disappears so quickly that it can hardly be inoculated with safety, the character of variola-vaccine lymph changes in the course of the next generation and assumes the milder serviceable properties of animal vaccine. Differences arise in the energy of individual lymph stocks. *Sacco*, for example, affirms that vaccine acts more mildly in Italy than in England, and *Woodville* in *Reports of a Series of Inoculation of the variola*

vaccine, describes such serious results from his inoculations, that it must be admitted, that his vaccine was variola-vaccine of the first or second generation.

To the question, how the formation of the abortive form may be presented, I can give no satisfactory answer; but can point out three facts:

1. Because cow-pox is generally found during the cooler season and because the cattle have a normal temperature about 2° C. higher than the human subject, the inoculated animals should be kept cool and be inoculated at some unprotected part of the body. (However the intensity with which a subject is affected with small-pox does not depend upon the elevation of the temperature of its body, for the hog which is not easily affected reach 38.8°, the sheep and goats 40°, man 37°, and the easily affected horses 37.6°, the calves 39.1°).

2. I hold very superficial incisions or scratches as the most proper way of transmission, because the superficial layers of the skin contribute most to the formation of pustules.

3. It is certainly important to observe closely and frequently the development of the efflorescence in order not to miss the right moment for obtaining the lymph. During the formation of the abortive forms it looks as if the germs might form pustules, if they were not constantly reäbsorbed, so that they cannot act upon the upper layers of the cutis (as if they were growing upon a seive). After having obtained immediate success in the first of my three inoculations, I thought I had obtained satisfactory results also at the second, when the protuberances which had appeared on the third day became papulæ with yellowish heads. In the hope that a richer pustule would develop, I put off taking the virus to the following day. There was then, nothing more to get; only pimples with non-infectious contents badly developed.

As to the use of cow-pox derived from variola, I advise patience, only the fourth or fifth generation can be altogether safe, moreover, the number of inoculation points should be limited, and not be set too closely.

Here, I believe, I have proved how active cow-pox may be obtained; the further modifications of cow-pox will be considered in the next section.

2. WEAKENING OF ANIMAL VACCINE.

I have intentionally not abridged my description of the inoculation of variola-vaccine from calf to calf, which I continued for months, because to my knowledge no similar observations had been either made or published, and because it throws light upon the variability of vaccine.

The degeneration or weakening of this very important substance, by many accepted as an axiom, by others rejected as mere fancy, has been much talked about since the earliest time of its use; yet only the few have had the time, the endurance and the opportunity of forming an independent opinion on the subject.

Some maintain that humanized vaccine produces still the same pustules, the same local and general symptoms, as at the time of Jenner, therefore, the same protective efficacity may be expected from it. If Jenner has overrated that efficacity when he maintained it to last the life time, he must have made a mistake, or drawn too hasty conclusions.

The opponents seek to prove, resting their assertions upon statistics which have been somewhat contradicted, that the protective power of the lymph has decreased, and maintain that it could not be otherwise since the local and general sequels of vaccination have assumed a milder type. It could not be expected to obtain so lasting a protection from the weaker processes as from the stronger vaccinal reaction observed in Jenner's time. Therefore, vaccine should be sought for in its progenitor and regenerated whenever the opportunity offers. Here, opinions diverge again. Some see the source of intensity only in the originality of the cow-pox found; only accidentally found cow-pox should be used for regeneration, say these. Others maintain that the greater energy of vaccine is to be found in the nature of the bovine race, for these reasons they hold to animal vaccine. I do not share the last opinion, although thoroughly convinced of the indispensability of animal vaccine. The protective value of every lymph stock (of the animal as well as the humanized) depends, according to my views, from the quality of its source, from the time that has elapsed since it left that source, and from the precautions used in propagating the lymph, but not from the animal or humanized quality of the lymph.

Nor does the apparent accidental nature of the origin of occa-

sionally found cow-pox offer the guarantee of especially good quality in the vaccine derived from it, for the different species of animals, which may give us vaccine are infected by the virus in a different manner, but never spontaneously, and the vaccine that may be communicated from one kind of animals to another, affects the bovine race with different degrees of intensity. As a rule the cause of cow-pox accidentally found cannot be proved, and it may have its origin in the manner described by Tschamer, or in another way. Sometimes, however, it originates from the hands of milkers that have just been vaccinated or re-vaccinated, and then as retro-vaccine it assumes a mild form. Vaccine originating in horse-pox may also act mildly if this horse-pox has been produced by vaccine in the hands of a vaccinated groom. But if the milker or groom were suffering from variola, we may expect in horse-pox and cow-pox the more energetic effects of variola-vaccine. There is no need of proving that the latter kind of cow-pox was present in Jenner's time; later, retro-vaccine may often enough have been found as cow-pox and gladly received and even have been induced by many premiums.

It is not generally known, although no new observation, that animal vaccine, suffers in the course of time a diminution in the length of the duration of its local symptoms. But the duration with which a virus acts locally on the surface to which it was applied, furnishes a standard of its intensity.

So that we may seek the greater energy of the virus in such pustules which with similar external appearance are active longer and form their scabs slower.

To this we have a proof in the pustules of varioloid and vaccination, which go through their processes much more quickly and do not produce a lymph so active in its generative qualities as variola and vaccine. So that if the pustule is produced quickly with active local reaction and disappears slowly we may conclude that there is present, an intense cause, which will have an active influence upon the body, and protect it efficaciously against new invasions.

The descriptions of newly produced variola-vaccine, as well as the contagiousness of the lymph were much greater than in later times. From my own observations I am satisfied that this cessation of local processes does not take place only in the first generations,

but continues later, very gradually, it is true, and in a manner which remains unnoticed by most vaccinating physicians. Such differences do not depend only upon cold or warm seasons or faulty generation, but also upon an actual weakening of the lymph.

This view does not correspond, to be sure, with the much contested opinion of the invariability of humanized lymph. Besides the fact, that we should first consider the question, why humanized vaccine does not produce variola again, we find also in the literature on the subject proofs that it assumes gradually somewhat milder forms if not in the symptoms, yet in the duration of the pustules. Compare the competent labors of *Steinbrenner, Bousquet, Triard, Rigal* and others in Parola, Vaccination, Vol. I, p. 416, seg. For example: Jenner's pustule required 17 days for dessicating, as long as cow-pox found in 1836 at Passy, which was inoculated on the arms of children. The scabs fell in both cases between the 23d and the 26th day. In 1844 the drying of the humanized Passy pustules took place in 14 days, that of Jenner's pustules which had been propagated 39 years, in twelve days. The latter had lost in these 39 years, five days of their ripening period, the Passy pustules in 8 years had lost three days.

Bousquet is altogether right when he says: He who recognizes no difference between humanized lymph stock, devised a long time ago from cow-pox, or one which has a similar but recent origin, has never inoculated cow-pox, or has been satisfied with the customary visit to the inoculated patient on the seventh day.

But I return to animal vaccine.

I was very much interested in the comparison of my new variola vaccine, with some originally animal vaccine, propagated by myself for seven years, and now already nearly 16 years old. Probably no lymph stock has ever been propagated longer and more carefully than this cow-pox found in 1865 at Beaugency. It was, at the time, inoculated on cows and calves in Paris, closely observed and compared with the pustules of vaccine coming originally from cow-pox which had been in use in Paris before, and had been brought from Naples and had been propagated 8 years (see *Lanoix: Dépaul, Gazette Médicale de Paris*, 1866, p. 164 and 319).

Although Dépaul declares, that he found no difference between the form and period of maturation of the pustule of these two

kinds of lymph, I think I can notice some differences from his definitions and those of Chauveau.

In the first place, Dépaul did not see at all the first three generations of the Beaugency vaccine, so that the more intense local symptoms may have already lost some of their intensity, when he, using vaccine of the fourth generation, did not begin his observations until the fifth. It produced after 3×24 hours small papula, the next day young pustules, which increased in size on the fifth and 6th day, and the drying of which began on the two succeeding days. From the 17th day the pustules began to fall. One after the other, 40 heifers were successfully inoculated. The taking of the virus generally occurred in 6×24 hours after inoculation. From the 28th generation, which matured very rapidly, virus could already be obtained on the third day after inoculation, from the 29th on the 5th, from the 30th on the 7th day. The last ten calves had the best pustules on the 5th day.

Chauvean says (Chauveau, Vaccine et Variole, p. 13 and 16) that the 8 years old Neapolitan lymph at that time matured pustules within five days, which increased in size until the eighth day and the scabs of which fell from the 14th to the 20th day. According to Dépaul, the drying began already on the 7th day. This is certainly a difference, for the scabs of the Naples pustules began to fall already on the 15th day, those of the fresh stock, not before the 17th day. Besides, the Beaugency lymph acted with uncommon, almost fearful intensity, in a similar manner then, as that described by Jenner of his cow-pox, while the Naples lymph did not produce such striking symptoms.

During the 16 years that have elapsed since then, the Beaugency lymph has been modified, its pustules run now through a shorter course, they mature in a medium temperature within four or five times 24 hours; on the 6th day they already become purulent, on the 7th day they are somewhat dry and the scabs fall from the 12th to the 16th day. This 16 years old vaccine takes then, now considerably quicker course than the 8 years old Naples lymph, and has, since its own origin, suffered a still more considerable loss, in the energy of its internal symptoms. We shall see also that the period of its greatest activity has been displaced. According to Dépaul, it produced at first, on the 5th, 6th, and 7th day when inoculated

from calf to calf, a fine pustule for almost every incision, once it was even used with good results on the third day, and it was then indifferent, whether it was inoculated with puncture or with incision. When I received that lymph ten years later from Rotterdam, whither it had come from Paris by the way of Brussels, I found the energy of the lymph used on the sixth day from calf to calf, maintained. Since then, it proves to be, on that day, still weaker, and I use it neither for calves, nor for people, when I can possibly avoid it. In the course of time I have experienced more failures after the inoculation of lymph of the fifth day, than formerly, and I cannot ascribe this merely to occasional failure if proper care in inoculation; and the surest results are now obtained with pustules of 4×24 hours after vaccination, then pretty young.

With this, it is not at all indifferent, whether we inoculate with punctures or with incisions, and the unexceptional success of every insertion, is no longer the rule even with lymph of 5×24 hours after inoculation.

Indeed our results in the use of animal lymph for the public, are more satisfactory than those reached by Dépaul, but then we inoculated differently, that is, by means of incisions or scratches. If we inoculated with punctures, as the French did then, our results would fall lamentably short.

I give here a table of the inoculations of calves in the Hamburg vaccine establishment, out of which may be seen, how different the vaccination value of the lymph is, according to the different stages of maturation.

Results of Inoculation on 732 Cases in the Vaccine Establishment of Hamburg, 1878 to 1881.

Inoculation with lymph from the Beaugency stock :	1878				1879				1880				1881				Total.		
		Result.				Result.				Result.				Result.					
	Calves.	Good.	Indifferent.	Bad.	Calves.	Good.	Indifferent.	Bad.	Calves.	Good.	Indifferent.	Bad.	Calves.	Good.	Indifferent.	Bad.	Calves.	Good.	Per Cent.
1. Preserved between plates	4	.....	1	3	9	3	4	2	20	12	.....	.....	9	5	4	.....	42	20	48
2. Fresh from calf to calf																			
On 3d day after inocula.	.....	.....	.....	.....	1	.....	1	.....	.....	.....	.....	.....	1	1	.....	.....	2	1	50
" 4th " " "	23	20 [87 p.c.]	2 [NB. 1]	1	32	23 [79 p.c.]	8 [NB. 3]	1	34	30 [86 p.c.]	1 [NB. 1]	3 [NB. 1]	28	24	4 [NB. 1]	.....	117	97	83
" 5th " " "	153	104 [68 p.c.]	47 [NB.11]	2	123	87 [71 p.c.]	30 [NB. 7]	6 [NB. 2]	117	81 [69 p.c.]	32 [NB. 7]	4 [NB. 1]	110	79	27 [NB. 2]	4	503	351	70
" 6th " " "	32	10	19 [NB. 5]	3 [NB. 1]	11	8	3	.....	4	2	2 [NB. 1]	.....	1	3	1	.....	51	23	45
" 7th " " "	.....	.....	.....	.....	2	1	1	.....	.....	.....	.....	.....	7	1	3	3	9	2	22
3. Retrovaccine fresh from the arm	.....	.....	.....	.....	2	2	.....	.....	3	3	.....	.....	3	3	.....	.....	8	8	100..
Totals	212	134	69 [NB.17]	9 [NB. 1]	180	124	47 [NB.10]	9 [NB. 2]	178	128	42 [NB. 9]	8 [NB. 2]	170	116	39 [NB. 3]	7	732	502	68..6

In explanation of this table, I must add that I consider the inoculation of a calf good, when almost all the pustules reach a satisfactory development, and as an indifferent result when only isolated groups of good pustules are formed. In the column, bad, I have placed the reaction which was altogether incomplete. The mark NB. means that with five calves the probable cause of failure of inoculation lay in the bad state of health of the subject.

In order to condense once more what I have said on the variation of this Beaugency stock, I report: The pustule grows now nearly as quickly as 16 years ago, but it soon gets purulent and the scabs fall off, on an average, four days earlier than they used to. The activity of the contents of the pustules, which formerly was greatest on the fifth, sixth and seventh day, and nearly unexceptionally sure, proves trustworthy now on the fourth and fifth days. On the sixth day the lymph is of little value, and almost so on the seventh day, and then is really not fit to be used.

On the other hand, my variola-vaccine had altogether the same properties as the young Beaugency cow-pox. Absolute energy of the lymph from the fifth to the seventh, and even to the eighth day; uncommonly well developed pustules, with limpid contents until the eighth and later until the seventh day drying slowly, and in the second generation casting their scabs only after 22 days, later from 17 to 18 days. *Ceely's* first variola-vaccine pustule did not come to development until the ninth day, and dried in 13 days. *Thiele* describes the maturation exactly like that of my second generation. *Reiter's* variola-vaccine pustule was destroyed on the sixth day for obtaining virus for inoculation, and *Scrofft* says that his reached its maximum on the sixth day.

From this it will be seen that with minor differences the phenomena of cow-pox and variola-vaccine agree with one another, and I think I can say beforehand, that my new lymph will in course of time run through the same phases as that of Beaugency.

I have mentioned that many authors are of opinion that humanized lymph degenerates, and that, therefore, we must turn to cow-pox or animal vaccine in order to obtain again, as the occasion offers, some efficacious protection. But from what has been said it will be seen that help is to be expected not from animal vaccine, but from originally active cow-pox; that animal vaccine suffers a loss of

energy much easier assignable than the humanized, and that it is, therefore advisable not to lay too much stress upon the old purity (nobility) of an animal lymph stock, but that it should be renewed (renovated) when the occasion presents.

It is true that it cannot be proved with certainty whether a young lymph stock has greater protective value than the older, but we may have a good opinion of it on account of its energetic activity. I hope I may be able to give later, a standard measure for the protective power of vaccine.

As a zealous promotor of animal vaccine, which has become indispensable to me, I will not insist again upon its usefulness, but, in conclusion, I will point out, that it should be regenerated betimes, in order that it may maintain its full energy. To me it seems that animal vaccine needs such regeneration quicker than the humanized.

The retro-vaccine which is less liked for reasons of opportunity and others, should be placed on an equality with an original animal vaccine of greater age, in its powers for producing greater quantities of lymph. With young regenerated animal lymph at one's disposal we can, however, do altogether without humanized lymph, even in cases when most may be expected from the latter, for it acts with more certainty, and may be preserved longer than that of older stock.

Indeed, this regeneration must take place with truly energetic cow-pox. He who accidentally finds cow-pox may judge of its value by the size and duration of the pustules, by the energy of the hold it takes when transplanted upon other cows and by its possible origin from variola. In the latter case it should, for precaution, be conveyed through a few cows before it is used on the human subject. —*Deutsche Vierteljahrsschrift für öffentliche Gesundheitspflege.*